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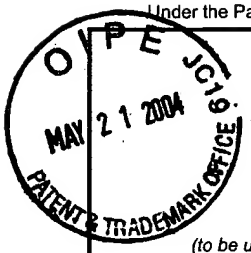

TRANSMITTAL FORM

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Total Number of Pages in This Submission

Application Number	**09/647,067**
Filing Date	**September 25, 2000**
First Named Inventor	**HSUEH, AARON, J.W.**
Group Art Unit	**1647**
Examiner Name	**BUNNER, BRIDGET E.**
Attorney Docket Number	**STAN-084**

ENCLOSURES (check all that apply)

- [x] Fee Transmittal Form
  - [ ] Fee Attached
- [ ] Amendment / Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Documents
- [ ] Response to Missing Parts/ Incomplete Application
  - [ ] Response to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Assignment Papers *(for an Application)*
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s
- [ ] After Allowance Communication to Group
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to Group *(Appeal Notice, Brief, Reply Brief)*
- [ ] Proprietary Information
- [ ] Status Letter
- [x] Other Enclosure(s) **IN TRIPLICATE:**
  1) **Appeal Brief (32 pgs.)**
  2) **Exhibits 1-4**
  3) **Figures 6A-6C**
  4) **Return Postcard**

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Signing Attorney/Agent (Reg. No.)	**PAULA A. BORDEN, 42,344** **BOZICEVIC, FIELD & FRANCIS LLP**
Signature	
Date	**May 21, 2004**

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FEE TRANSMITTAL for FY 2004

Effective 10/01/2003. Patent fees are subject to annual revision.

☒ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT **($) 1,170.00**

Complete if Known	
Application Number	09/647,067
Filing Date	September 25, 2000
First Named Inventor	HSUEH, AARON, J.W.
Examiner Name	BUNNER, BRIDGET E.
Art Unit	1647
Attorney Docket No.	STAN-084

METHOD OF PAYMENT (check all that apply)

☐ Check ☐ Credit Card ☐ Money Order ☐ Other ☐ None

☒ Deposit Account:
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FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	770	2001	385	Utility filing fee	
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	
				SUBTOTAL (1)	0.00

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

	Extra Claims		Fee from below		Fee Paid
Total Claims	-20** =		x	=	
Indep. Claims	-3** =		x	=	
Multiple Dependent				=	

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	86	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) $ 0.00

***or number previously paid, if greater; For Reissues, see above.*

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge – late filing fee or oath	
1052	50	2052	25	Surcharge – late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examination action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	420	2252	210	Extension for reply within second month	
1253	950	2253	475	Extension for reply within third month	
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	1,005.00
1401	330	2401	165	Notice of Appeal	165
1402	330	2402	165	Filing a brief in support of an appeal	
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive – unavoidable	
1453	1,330	2453	665	Petition to revive – unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1406	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	2809	385	Filing a submission after final rejection (37 CFR § 1.129(a))	
1810	770	2810	385	For each additional invention to be examined (37 CFR § 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify) _____

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SUBMITTED BY		Complete (*if applicable*)			
Name (Print/Type)	Paula A. Borden	Registration No. (Attorney/Agent)	42,344	Telephone	(650) 833-7710
Signature				Date	05/21/2004

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APPELLANTS' BRIEF	Attorney Docket Confirmation No.	STAN084 3881
	First Named Inventor	A. Hsueh
	Application Number	09/647,067
	Filing Date	Sept. 25, 2000
	Group Art Unit	1647
Address to: Mail Stop Appeal Brief-Patents Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Examiner Name	B.E. Bunner
	Title	*Novel mammalian G-protein coupled receptors having extracellular leucine rich repeat regions*

Sir:

This Brief is filed in support of Appellants' appeal from the final Office Action dated April 23, 2003. No claims have been allowed, and claims 1, 2, 4, 7-11, and 18-20 are pending. Claims 1, 2, 4, 7-11, and 18-20 are appealed. A Notice of Appeal was filed on October 22, 2003.

The Board of Appeals and Interferences has jurisdiction over this appeal pursuant to 35 U.S.C. §134.

The Commissioner is hereby authorized to charge deposit account number 50-0815 in the amount of $165.00 to cover the fee required under 37 C.F.R. §1.17(c) for filing Appellants' brief, and the $1005.00 for the extension of time. In the unlikely event that the fee transmittal or other papers are separated from this document and/or other fees or relief are required, appellants petition for such relief, including extensions of time, and authorize the Commissioner to charge any fees under 37 C.F.R. §§ 1.16, 1.17 and 1.21 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815, order number STAN084.

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01 FC:2402 165.00 DA
05/25/2004 AWONDAF1 00000038 500815 09647067
02 FC:2255 1005.00 DA

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REAL PARTY IN INTEREST

The inventors listed on this patent application are Aaron J.W. Hsueh, Sheau Yu Hsu, Shan-Guang Liang, and Petrus J. van der Spek. Aaron J.W. Hsueh, Sheau Yu Hsu, Shan-Guang Liang assigned their entire rights in the invention to The Board of Trustees of the Leland Stanford Junior University. Petrus Johannes Van Der Spek assigned his entire rights in the invention to Akzo Nobel N.V.

RELATED APPEALS AND INTERFERENCES

There are currently no other appeals or interferences known to Appellant, the undersigned Appellants' representative, or the assignee to whom the inventors assigned their rights in the instant case, which would directly affect or be directly affected by, or have a bearing on the Board's decision in the instant appeal.

STATUS OF THE CLAIMS

This application is a national phase filing under 35 U.S.C. §371 of International Patent Application No. PCT/US99/06573, filed March 25, 1999, which application claims benefit of priority to U.S. Provisional Patent Application No. 60/079,501, filed March 26, 1998.

Claims 1-18 were originally filed on September 25, 2000. In response to a Restriction Requirement mailed March 11, 2002, Group A claims (claims 1-11, and 18) were elected for prosecution on the merits. In an amendment, filed on February 3, 2003 and responsive to the Office Action mailed November 6, 2002, claims 3, 5, and 6 were canceled; and claims 1, 2, 4, 7, 10, 11, and 18 were amended; and the claim amendments were entered. In an amendment, filed on October 22, 2003 and responsive to the April 23, 2003 final Office Action, claims 2, 4, and 7 were amended; claims 12-17 were canceled; and claims 19 and 20 were added. The Advisory Action, mailed on November 12, 2003 indicated that, for purposes of Appeal, the amendments made in the amendment, filed on October 22, 2003 and responsive to the April 23, 2003 final Office Action, will be entered.

As a result of the amendments discussed above, claims 1, 2, 4, 7-11, and 18-20 remain pending.

All of the pending claims 1, 2, 4, 7-11, and 18-20 shown in attached Appendix I remain pending, rejected, and appealed here.

STATUS OF AMENDMENTS

During the course of prosecution, the following amendments were made.

Claims 1-18 were originally filed on September 25, 2000. In response to a Restriction Requirement mailed March 11, 2002, Group A claims (claims 1-11, and 18) were elected for prosecution on the merits. In an amendment, filed on February 3, 2003 and responsive to the Office Action mailed November 6, 2002, claims 3, 5, and 6 were canceled; and claims 1, 2, 4, 7, 10, 11, and 18 were amended; and the claim amendments were entered. In an amendment, filed on October 22, 2003 and responsive to the April 23, 2003 final Office Action, claims 2, 4, and 7 were amended; claims 12-17 were canceled; and claims 19 and 20 were added. The Advisory Action, mailed on November 12, 2003 indicated that, for purposes of Appeal, the amendments made in the amendment, filed on October 22, 2003 and responsive to the April 23, 2003 final Office Action, will be entered.

SUMMARY OF THE INVENTION

The instant invention as claimed relates to the identification and characterization of G-protein coupled receptors (GPCR), termed "LGR4," "LGR5," and "LGR7." These new G-protein coupled receptors are similar to other, previously known GPCR in that they exhibit the characteristic seven transmembrane feature. However, LGR4, LGR5, and LGR7 differ from the vast majority of known GPCR in that they further exhibit a large extra-cellular leucine-rich repeat region. Specification, page 3, lines 26-29. The extra-cellular leucine-rich repeat region found in LGR4, LGR5, and LGR7 is structurally similar to that found in the previously described leutinizing hormone (LH), follicle stimulating hormone (FSH), and thyrotropin (TSH) receptors. Specification, page 3, line 29 to page 4, line 1; and page 1, lines 13-19. The large extracellular, leucine-rich domain of the LH, FSH, and TSH receptors, which domain is also referred to as an ectodomain, is believed to bind the corresponding hormone ligand. Specification, page 1, lines 13-19.

Nucleic acids encoding mammalian LGR7 polypeptides are useful for producing LGR7 polypeptides. Specification, page 9, lines 20-27. The extracellular domain of a subject GPCR, e.g., LGR7, is useful for drug screening for agonists and antagonists. Specification, page 11, lines 1-2. The solubilized extracellular domain of a subject GPCR, e.g., LGR7, is useful for as a therapeutic agent, e.g., in the neutralization of the action of an endogenous ligand. Specification, page 11, lines 3-4; and page 21, lines 12-15.

As discussed in the specification, the inventors identified a human LGR4 cDNA (SEQ ID NO:01), which encodes an LGR4 protein (SEQ ID NO:2); a human LGR5 cDNA (SEQ ID NO:03), which encodes an LGR5 protein (SEQ ID NO:04); and two human LGR7 cDNAs (SEQ ID NO:05 and SEQ ID NO:07) which encode LGR7 proteins (SEQ ID NO:06 and SEQ ID NO:08, respectively). Specification, page 4, lines 4-5, lines 8-9, and lines 18-20; Figure 5; page 25, lines 15-25. The specification discusses various polypeptide fragments of LGR7. Specification, page 9, line 5 to page 11, line 17.

The invention thus provides new members of a very small subset of GPCR, which subset share the feature of a large ectodomain, and which subset includes peptide hormone-binding receptors. As noted above, like other previously identified members of this small subset of GPCR, LGR7 proteins are identified in the specification as hormone-binding receptors. Further, as noted above, the specification asserts that the solubilized extracellular domain is useful for as a therapeutic agent, e.g., in the neutralization of the action of an endogenous ligand; and for identifying ligands (e.g., agonists and antagonists) of the receptor.

ISSUES

There are three issues on appeal, as follows:

I. WHETHER CLAIMS 1, 2, 4, 7-11, AND 18-20 MEET THE UTILITY REQUIREMENT OF 35 U.S.C. §101;

II. WHETHER CLAIMS 1, 2, 4, 7-11, AND 18-20 MEET THE ENABLEMENT REQUIREMENT OF 35 U.S.C. §112, FIRST PARAGRAPH; AND

III. WHETHER CLAIMS 1, 2, 4, 8-11, AND 18-20 MEET THE WRITTEN DESCRIPTION REQUIREMENT OF 35 U.S.C. §112, FIRST PARAGRAPH.

GROUPING OF THE CLAIMS

Claims 1, 2, 4, 7, 19, and 20 are directed to an isolated nucleic acid encoding an LGR7 protein; claim 8 is directed to an expression cassette comprising a nucleic acid according to claim 1; claim 9 is directed to a cell comprising an expression cassette according to claim 8; claim 10 is directed to a method for producing an LGR7 protein; claim 11 is directed to a purified polypeptide composition comprising an LGR7 protein; and claim 18 is directed to a method for screening a sample for the presence of a ligand for an LGR7 protein. Claims 1, 2, 4, 7-11, and 18-20 are argued as a group. With respect to the utility rejection under 35 U.S.C.§101, the enablement rejections under 35 U.S.C.§112, first paragraph, and the written description rejection under 35 U.S.C.§112, first paragraph as set forth in the April 23, 2003 final Office Action, claims 1, 2, 4, 7-11, and 18-20 are argued as a group and stand or fall together.

ARGUMENTS

The arguments portion of this Brief is divided into two sections. The first section describes Appellants' understanding of the Examiner's rejections. The second section specifically addresses the three issues outlined above relating to whether the claimed invention meets the utility requirement of 35 U.S.C. §101; whether the claimed invention meets the enablement requirement of 35 U.S.C.§112, first paragraph; and whether the claimed invention meets the written description requirement of 35 U.S.C.§112, first paragraph.

THE EXAMINER'S REJECTIONS

Rejection under 35 U.S.C.§101

Claims 1, 2, 4, 7-11, and 18-20 were rejected under 35 U.S.C. §101 as allegedly lacking utility. In support of this rejection, the Office argued that the rejected claims are not supported by either a specific and substantial asserted utility or a well established utility.

Rejections under 35 U.S.C.§112, first paragraph

Enablement

i) Claims 1, 2, 4, 7-11, and 18-20 were rejected under 35 U.S.C.§112, first paragraph, as allegedly lacking enablement. In support of this rejection, the Office argued that since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention.

ii) Claims 1, 2, 4, 8-11, and 18-20 were rejected under 35 U.S.C.§112, first paragraph, as allegedly lacking enablement. In support of this rejection, the Office argued that the specification does not teach the functional characteristics of LGR7 or any polynucleotide variants; and that undue experimentation would be required by the skilled artisan to generate the infinite number of LGR7 variants recited in the claims and to screen the same for activity.

Written description

Claims 1, 2, 4, 8-11, and 18-20 were rejected under 35 U.S.C.§112, first paragraph, as allegedly lacking written description. In support of this rejection, the Office argued that the rejected claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, has possession of the claimed invention.

APPELLANTS' RESPONSE TO THE REJECTIONS

Rejection under 35 U.S.C.§101

The rejection of claims 1, 2, 4, 7-11, and 18-20 under 35 U.S.C.§101 is in error. The claimed nucleic acids have a well-established utility. The asserted utilities of use of the nucleic acids to provide the encoded proteins; the use of the encoded proteins to identify ligands (e.g., agonists and antagonists); and the use of the ectodomain portion of the encoded proteins in the neutralization of the action of an endogenous ligand are well established utilities. In view of the structural similarity of LGR7 to a small family of peptide hormone-binding GPCR, the asserted utilities for the claimed invention are well established.

Rejections under 35 U.S.C.§112, first paragraph

Enablement

i) The rejection of claims 1, 2, 4, 7-11, and 18-20 under 35 U.S.C.§112, first paragraph, as lacking enablement, is in error. As noted above, the asserted utilities of use of the nucleic acids to provide the encoded proteins; the use of the encoded proteins to identify agonists and antagonists; and the use of the ectodomain portion of the encoded proteins in the neutralization of the action of an endogenous ligand are well established utilities. Accordingly, those skilled in the art would know how to make and use the claimed invention.

ii) The rejection of claims 1, 2, 4, 8-11, and 18-20 under 35 U.S.C.§112, first paragraph, as lacking enablement, is in error. The specification provides ample description as to how to make and use the claimed nucleic acids and polypeptides. The specification provides ample description of how to produce an LGR7 protein encoded by the nucleic acids. The specification provides ample description of how to screen a sample for the presence of an LGR7 ligand. Accordingly, the specification, and consequently claims 1, 2, 4, 8-11, and 18-20, are in compliance with the enablement requirement of 35 U.S.C.§112, first paragraph.

Written description

The rejection of claims 1, 2, 4, 8-11, and 18-20 under 35 U.S.C.§112, first paragraph, as lacking written description, is in error. The instant specification provides the nucleotide and amino acid sequences of an adequate number of species, such that those skilled in the art would have recognized that Appellants had possession of the claimed invention as of the priority date. In view of such, claims 1, 2, 4, 8-11, and 18-20 meet the written description requirement of 35 U.S.C.§112, first paragraph.

I. WHETHER CLAIMS 1, 2, 4, 7-11, AND 18-20 MEET THE UTILITY REQUIREMENT OF 35 U.S.C. § 101

The April 23, 2003 final Office Action rejected claims 1, 2, 4, 7-11, and 18-20 under 35 U.S.C. § 101 as allegedly lacking utility. The April 23, 2003 final Office Action stated that novel biological molecules lack well established utility and must undergo extensive experimentation. The April 23, 2003 final Office Action stated that the asserted utilities are credible, but not specific or substantial. The rejection of claims 1, 2, 4, 7-11, and 18-20 as allegedly lacking utility is in error.

The Utility Examination Guidelines (Federal Register 66, No. 4, January 5, 2001; hereinafter the "Utility Guidelines") provides instructions for examining patent applications for compliance with the utility requirement of 35 U.S.C. § 101.[1] The Utility Guidelines provides a "Utility Review Flowchart" for reviewing patent applications for compliance with the utility requirement of 35 U.S.C. § 101.[2]

The utility requirements under 35 U.S.C.§101 are also discussed in the Manual of a Patent Examining Procedure (MPEP) §2107. MPEP § 2107 provides that "if at any time during the examination, it becomes readily apparent that the claimed invention has a well-established utility, do not impose a rejection based on lack of utility."[3] Moreover, this provision is also reflected in the Utility Review Flowchart, which states that if an invention does have a well established utility, a rejection under § 101 shall not be made.[4]

1 Utility Examination Guidelines (Federal Register 66, No. 4, January 5, 2001), [hereinafter "The Utility Guidelines"].
2 *Id.* at page 9.
3 MPEP § 2107, "II Examination Guidelines for the Utility Requirement".
4 The Utility Guidelines, page 9.

Well established utility is defined in the Utility Guidelines as a "well known, immediately apparent, or implied by the specification's disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art."[5]

The utility requirement of 35 U.S.C.§101 may be satisfied in one of two ways. 1) A claimed invention may have a well-established utility, in which case the well-established utility is assumed to be specific, substantial, and credible. A well-established utility is present if the claimed invention has a specific, substantial, and credible utility that would have been readily apparent to one of skill in the art in view of the disclosure, alone or taken with the knowledge of one skilled in the art. 2) Where a claimed invention does not have an apparent well-established utility, the utility requirement can be established by specifically examining the specific, substantial, and credible utility of the claimed invention.

The rejection of claims 1, 2, 4, 7-11, and 18-20 under 35 U.S.C. § 101 is discussed in view of the Utility Review Flowchart and MPEP §2107.

The claimed invention has a well established utility.

The instant invention as claimed has a well-established utility and therefore meets the utility requirement of 35 U.S.C. § 101.

The Utility Guidelines provide numerous training examples with various hypothetical scenarios in order to assist in a determination of whether a claimed invention has a well-established utility or, in the absence of a well-established utility, has at least one asserted utility that is specific, substantial, and credible.[6] The facts of the present application are similar to those of the hypothetical scenario described in Example 10 of the Utility Guidelines, wherein the analysis determined that the application did indeed provide the requisite well-established utility.

5 The Utility Guidelines, at page 7.
6 *Id.* at pages 13-74.

In pertinent part, Example 10 of the Utility Guidelines provides the following hypothetical scenario:

> The specification discloses a Table that indicates that one member of the library having SEQ ID NO: 2 has a high level of homology to a DNA ligase. The specification teaches that this complete ORF (SEQ ID NO: 2) encodes SEQ ID NO: 3. An alignment of SEQ ID NO: 3 with known amino acid sequences of DNA ligases indicates that there is a high level of sequence conservation between the various known ligases. The overall level of sequence similarity between SEQ ID NO: 3 and the consensus sequence of the known DNA ligases that are presented in the specification reveals a similarity score of 95%. A search of the prior art confirms that SEQ ID NO: 2 has high homology to DNA Ligase encoding nucleic acids and that the next highest level of homology is to alpha-actin. However, the latter homology is only 50%. Based on the sequence homologies, the specification asserts that SEQ ID NO: 2 encodes a DNA ligase.[7]

Based on these facts, the analysis provided in the Utility Guidelines concludes the following:

> there is no reason to doubt the assertion that SEQ ID NO: 2 encodes a DNA ligase. Further, DNA ligases have a well-established use in the molecular biology art based on this class of protein's ability to ligate DNA.
>
> * * *
>
> ***Note that if there is a well-established utility already associated with the claimed invention, the utility need not be asserted in the specification as filed.*** In order ***to determine whether the claimed invention has a well-established utility the examiner must determine that the invention has a specific, substantial and credible utility that would have been readily apparent to one of skill in the art.***[8]

A similar analysis and conclusion applies to the instant invention as claimed. The LGR7 nucleic acids and encoded polypeptides are structurally similar to a small, well-known group of GPCR that bind peptide hormones, e.g., the TSH receptor, the LH receptor, and the FSH receptor. Peptide hormone receptors have a well-established use in the art. Based on the disclosed close structural similarity of LGR7 to known peptide hormone-binding GPCR, LGR7 also has a well-established utility.

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7 *Id.* at 53.
8 The Utility Guidelines, at pages 54-55.

The claimed invention has a well-established utility that would have been readily apparent to one of skill in the art, given the instant disclosure, alone or taken with the knowledge of one skilled in the art.

In the present application, on page 3, lines 26-29, the specification states that the disclosed LGR7 polypeptides are novel mammalian G protein coupled receptor (GPCR), characterized by the presence of extracellular leucine rich repeat regions. In addition, the specification also states that LGR7 polypeptides function as a GPCR. Moreover, the specification also states on page 9, lines 20-27, that nucleic acids encoding mammalian LGR7 polypeptides are useful for producing LGR7 polypeptides, which polypeptides are asserted to function as GPCR, and on page 21, lines 12-15, the specification states that the ***LGR7 ligand is a hormone.***

The specification further states on page 11, lines 3-4; and page 21, lines 12-15, that the extracellular domain can be solubilized ***and used to neutralize the activity of the endogenous ligand*** (e.g., a hormone.) In addition, the specification states on page 11, lines 1-4; page 20, lines 8-14; and page 2, lines 13-14, that the LGR7 polypeptides are useful ***for identification of a ligand for the GPCR; for screening for agonists and antagonists***.

The claimed nucleic acids are thus useful for producing LGR7 polypeptides, which polypeptides are hormone receptors, and are useful for screening for ligands (e.g., agonists and antagonists), and for the generation of soluble binding proteins for the neutralization of the action of an endogenous ligand. Accordingly, based on the specification, one of skill in the art would readily appreciate the well-established utility of the claimed polynucleotides.

As discussed during an Examiner Interview, which took place on October 9, 2003, the LGR-type GPCR are not like other (non-LGR-type) GPCR. First, the LGR disclosed in the instant application include, in addition to the 7 transmembrane structure typical of other GPCR, a leucine-rich extracellular domain at

the amino terminus of the protein.[9] This amino-terminal extracellular domain with leucine-rich repeats is referred to in the specification as an "ectodomain" to emphasize the fact that it is extracellular.[10]

The ectodomain of the LGR proteins is over 300 amino acids in length; the leucine rich repeat portion of the ectodomain is approximately 200 amino acids in length; and the 7 transmembrane region is approximately 250 amino acids in length. See, e.g., Figure 6 of the instant specification; and Exhibits 2-4, provided along with an amendment filed on October 22, 2003 and responsive to the April 23, 2003 final Office Action. Copies of Figure 6 and Exhibits 2-4 are provided herewith for convenience.

Apart from the LGR-type GPCR, ***no other GPCR*** has such an ectodomain. This striking difference is illustrated in the accompanying figure entitled "Schematic representation of functional domains in LGR family receptors," which was provided as Exhibit 1 along with an amendment filed on October 22, 2003 and responsive to the April 23, 2003 final Office Action. A copy of Exhibit 1 is provided herewith for convenience.

Other than LGR-type GPCRs, GPCR typically ***do not have*** an amino-terminal ectodomain that can be expressed as soluble proteins and used to neutralize the activity of an endogenous hormone ligand. This particular asserted utility of LGR-type GPCR is thus *specific* to LGR-type GPCR.

As illustrated on the world wide web site receptome.stanford.edu, there are **hundreds** of GPCR with the typical 7 transmembrane structure. In contrast, ***fewer than 10*** mammalian LGR-type GPCR had been identified as of the priority date of the instant application.

As further discussed during the October 9, 2003 Examiner Interview, and as illustrated in Exhibits 1-4, the disclosed LGR-type GPCR have an overall structure that is very similar to luteinizing hormone receptor (LHR), follicle stimulating hormone receptor (FSHR; also referred to in the art as "follitropin

9 Specification, page 3, line 30 to page 4, line 1.
10 *Id.* at page 25, lines 18-19.

receptor"), and thyroid stimulating hormone receptor (TSHR).[11] LHR, FSHR, and TSHR were known in the art as of the priority date of the instant application. ***All three are hormone receptors***. The relationship between LGR-type GPCR and other GPCR, and among LGR-type GPCR, is illustrated in Figure 3 of Hsu et al. ((2000) *Molec. Endocrinol.* 14:1257-1271; "Hsu (2000)," a copy of which was provided as Exhibit 2 in the amendment, filed on February 3, 2003 and responsive to the November 6, 2002 Office Action.

As discussed during the October 9, 2003, Examiner Interview, the analysis of LGR7 was conducted based on its structural similarity to human LHR, FSHR, and TSHR. As discussed in Hsu (2000), features of the LGR7 could be identified based on the structural similarity to LHR. Hsu (2000) states that, based on an alignment of the LGR7 amino acid sequence with those of LHR and TSHR, two different point mutations were made in LGR7 that affected its function as a GPCR. Hsu (2000), page 1261, column 2, second full paragraph, to page 1263, column 2, end of Results section. Thus, the function of LGR7 was determined based on its close structural similarity to LHR and TSHR.

The fact that LGR7 bears a ***close structural relationship*** to the previously known LGR-type GPCRs LHR and TSHR is illustrated in the alignments depicted in Exhibit 2-4, copies of which are provided herewith. Exhibit 2 provides an amino acid sequence alignment of LGR7 with LHR. Exhibit 3 provides an amino acid sequence alignment of LGR7 with TSHR. Exhibit 4 provides an amino acid sequence alignment of LGR7 with TSHR, which alignment shows the locations of leucine-rich repeats (LRR). Exhibits 2-4 highlight the overall structural similarities among LGR-type GPCR, and between LGR7 and other LGR-type GPCR.

Similar to the DNA ligase comparison in Example 10 of the Utility Guidelines, the claimed nucleic acids share a striking structural similarity to a small, distinct set of well-characterized and well-understood hormone receptors. As such, once the claimed nucleic acids of the present invention, and their striking structural similarity to the other small class of LGR-type GPCR, were disclosed, their utility would have been apparent to one of skill in the art. Accordingly, akin to the hypothetical scenario of Example 10

11 *Id.* at page 3, lines 29-30.

presented in the Utility Guidelines, a well-established utility was already associated with the claimed nucleic acids and polypeptides of the present invention, as would have been readily apparent to one of skill in the art.

The data presented in Hsu (2002) provide further evidence for the fact that, as asserted in the specification, LGR7 is a GPCR and binds a hormone.

As discussed during the October 9, 2003 Examiner Interview, the disclosed LGR7 polypeptide, like LHR, FSHR, and TSHR, binds a hormone, functions as a GPCR, and has signal transduction properties similar to those of LHR. Indeed, on page 21, lines 12-15, the instant specification asserts that ***LGR7 is a hormone receptor***.

The fact that the instant claims are supported by a well-established utility is further demonstrated in Hsu et al. ((2002) *Science* 295:671-674; "Hsu (2002)", a copy of which was provided as Exhibit 1 along with the amendment, filed on February 3, 2003 and responsive to the November 6, 2002 Office Action), a publication co-authored by inventors Sheau Y. Hsu and A.J.W. Hsueh. Hsu (2002) states that LGR7 binds the hormone relaxin, and that relaxin activates adenylate cyclase through G_S proteins upon relaxin binding. Hsu (2002), page 672, column 1, last paragraph; and Figure 1. Thus, Hsu (2002) provides further evidence for the fact that, as asserted, LGR7 functions as a GPCR, and ***is a hormone receptor***.

The data presented in Hsu (2002) provide further evidence for the fact that, as asserted in the specification, the solubilized ectodomain of LGR7 is useful to neutralize the activity of an endogenous hormone ligand of LGR7.

The instant specification asserts that solubilized LGR7 ectodomain is useful to neutralize the activity of the endogenous hormone ligand of LGR7. The specification, on page 21, lines 12-15, asserts that the ectodomain of LGR7 can be used to neutralize the activity of an endogenous hormone ligand of LGR7. As discussed above, this particular well-established utility is specific to LGR-type GPCR, i.e., it would not apply to *any* GPCR, but to a very small, specific subset of GPCR which share the ectodomain feature.

Hsu (2002) states that 7BP, a soluble ectodomain of LGR7, antagonizes the action of the endogenous hormone ligand of LGR7, i.e., relaxin. Hsu (2002), page 673, Figure 4; and column 2. Thus, Hsu (2002) demonstrates that LGR7 is useful for the generation of functional binding proteins that neutralize the action of an endogenous hormone ligand of LGR7, as asserted in the instant specification.

The Examiner has not met the initial burden to establish a prima facie case of lack of well-established utility.

In the Advisory Action (as well as in previous Office Actions), the Examiner stated that "[N]ovel biological molecules lack well established utility and must undergo extensive experimentation." Advisory Action, page 2. The Examiner has provided no basis in reasoning for such a statement. Such a sweeping general statement is insufficient to establish that a claimed invention lacks a well established utility. As stated in MPEP §2107.01, it is imperative that Office personnel use specificity in setting forth an initial rejection under 35 U.S.C.§101 and support any factual conclusions made in the *prima facie* showing. In asserting that novel biological molecules lack well established utility and must undergo extensive experimentation, the Examiner has swept the "well-established utility" question away in one sentence without any explanation or well-reasoned statements. Such is not a proper analysis of the utility requirement of 35 U.S.C.§101.

Indeed, the Utility Guidelines make no such statement that "novel biological materials lack well-established utility." For example, in Example 10 of the Utility Guidelines, the exemplary DNA ligase-encoding nucleic acid may well be a novel biological material and still be deemed to have a well-established utility.

Conclusion

As presented above, in view of the fact that LGR7 polypeptides were shown to belong to a very small, distinct subset of GPCR with well-known and well-established functions (and therefore specific, substantial, and credible utility), the utility of the claimed invention would have been readily apparent to one of skill in the art in view of the disclosure, alone or taken with the knowledge of one skilled in the art. In

summary, the instant invention as claimed has a well-established utility, because the claimed invention has a specific, substantial, and credible utility that would have been readily apparent to one of skill in the art in view of the disclosure, alone or taken with the knowledge of one skilled in the art.

The claimed invention has at least one specific, substantial, and credible asserted utility

Even if one were to take the position, as the Examiner has done, that the claimed invention does not have a well established utility, and Appellants do not take this position, the specification of the present application does make an assertion of at least one utility for the claimed invention that is specific, substantial, and credible. The April 23, 2003 final Office Action stated that the asserted utilities are credible, but not specific or substantial. Thus, the Examiner acknowledged that at least one asserted utility is credible. Appellants submit that the specification provides at least one utility for the claimed invention that is specific and substantial.

The Utility Guidelines provide Example 12 as an aid for determining whether an asserted utility for an invention is specific, substantial and credible. Example 12 poses a hypothetical situation in which an applicant files an application that discloses, in pertinent part, the following:

> a protein, isolated from a cell membrane preparation, which is the binding partner for protein X. The specification does not characterize the isolated protein with regard to its biological function or any disease or body condition that is associated with the isolated protein. Based solely on the fact that the protein was isolated from a cell membrane and it binds to protein X, applicant characterizes the isolated protein as receptor A. The function of protein X has also not been identified. The specification discloses a binding assay for determining other materials which bind to the receptor...[12]

The Utility Guidelines conclude that in the hypothetical scenario of Example 12 specific utility is present for claims directed to the isolated receptor, as well as methods for identifying materials which bind

12 The Utility Guidelines, at page 63.

to the receptor.[13] The specific utility in such a hypothetical scenario was based on the observation that "the methods are not applicable to the general class of receptors."[14]

Analogous to Example 12 of the Utility Guidelines, the present application states on page 11, lines 3-4; and page 21, lines 12-15, that the extracellular domain can be solubilized ***and used to neutralize the activity of the endogenous ligand*** (e.g., a hormone.) In addition, the specification states on page 11, lines 1-4; page 20, lines 8-14; and page 2, lines 13-14, that the LGR7 polypeptides are useful for identification of a ligand for the GPCR; for screening for agonists and antagonists. Accordingly, akin to the analysis of Example 12 of the Utility Guidelines, methods of identifying materials which bind to claimed receptors of the present application *are not applicable to the general class of receptors*. Instead, as discussed in ample detail above, LGR7 belongs to a small, distinct subset of GPCR with well-known functions. Therefore, there is an asserted specific utility for the claimed invention.

However, with respect to substantial utility, the analysis of Example 12 of the Utility Guidelines concludes that the substantial utility is not present because no information was provided on the receptor or the compounds that binds the receptor.

In contrast to the hypothetical scenario of Example 12 of the Utility Guidelines, the present application, on page 3, lines 26-29, asserts that the human LGR7 polypeptide is a novel mammalian GPCR, characterized by the presence of extracellular leucine rich repeat regions, and as such belongs to a small subset of GPCR, including hormone-binding GPCR. In addition, the specification also asserts that the LGR7 polypeptide functions as a GPCR. Moreover, the specification also states on page 9, lines 20-27, that nucleic acids encoding mammalian LGR7 polypeptides are useful for producing LGR7 polypeptides, which polypeptides are asserted to function as GPCR, and on page 21, lines 12-15, the specification asserts that the ***LGR7 ligand is a hormone***.

13 The Utility Guidelines, at page 65-67.
14 *Id.* at page 67.

Accordingly, unlike the hypothetical receptor of Example 12 presented in the Utility Guidelines, the instant specification does indeed disclose information regarding the receptor, the endogenous ligand for the receptor, as well as a context for use of the receptor. Therefore, the present application does assert a substantial utility.

Example 12 of the Utility Guidelines further notes a caveat, i.e., that if the specification also discloses information on the receptor, the analysis would be changed since a well-established utility for the claimed receptor would be apparent.[15] As noted above, unlike the hypothetical scenario of Example 12 of the Utility Guidelines, the present specification discloses ample information on the claimed receptor and its ligand. Therefore, as concluded above, a specific, substantial, and credible utility is present for the claimed invention.

The Final Office Action has not established a *prima facie* case for lack of utility

As set forth in MPEP§2107.01, the Office must A) make a *prima facie* showing that the claimed invention lacks utility; and B) provide a sufficient evidentiary basis for factual assumptions relied upon in establishing the *prima facie* showing. The Patent Office must set forth factual reasons which would lead one skilled in the art to question the objective truth of the statement of operability. The *prima facie* showing must be set forth in a well-reasoned statement. The statement must articulate sound reasons why a person of ordinary skill in the art would conclude that it is more likely than not that an asserted utility is not credible. The statement should specifically identify the scientific basis of any factual conclusions made in the *prima facie* showing. The statement must also explain why any evidence of record that supports the asserted utility would not be persuasive to one of ordinary skill.

It is well established that "a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of §101 for the entire claimed subject matter unless there is a reason for the skilled in the art to question the

15 The Utility Guidelines, page 70.

objective truth of the statement of utility or its scope." *In re Langer* 183 USPQ 288, 297 (CCPA 1974) (emphasis in original).

The final Office Action stated that although Hsu (2000) demonstrate that LGR7 could be utilized to identify relaxin, the specification does not suggest this utility. However, as noted above, the specification states that an LGR7 protein binds a hormone. In view of the structural similarity of LGR7 to other GPCR ***that share the feature of having a large ectodomain*** and ***that bind hormone ligands***, the utility would have been readily apparent to one of skill in the art in view of the disclosure, alone or taken with the knowledge of one skilled in the art.

The Advisory Action stated that, "although the specification of the instant application teaches that LGR-7 has an ectodomain, there is no disclosure of the location of the ectodomain with LGR7's amino acid sequence or as to how long it is." Advisory Action, page 2. However, Exhibits 2-4, which were previously provided to the Examiner, show the position of the ectodomain of LGR7. Figure 6 as filed with the application shows the position of the ectodomain in LGR4 and LGR5. The amino acid sequences of LHR, FSHR, and TSHR were known as of the filing date of the instant invention. Thus, there was ample guidance in the specification that would have allowed any person skilled in the art to perform the same amino acid sequence alignment as provided in Exhibits 2-4, compare such alignments with those depicted in Figure 6 as filed, and identify the position of the ectodomain of LGR7. Indeed, Figure 2 of Hsu (2000) provides an amino acid sequence alignment of LGR7, points out the leucine-rich repeats that are characteristic of the ectodomain, and shows the site of the beginning of the first transmembrane domain, thereby delineating the ectodomain. Anyone skilled in the art, given the amino acid sequences provided in the instant specification, the publicly available LHR, FSHR, and TSHR amino acid sequences, and using Figure 6 as a guide, could have readily identified the ectodomain of LGR7.

The Advisory Action further stated that the specification discloses nothing specific about LGR7's hormone ligand. However, as discussed above in detail, the total number of LGR-type GPCR that were known as of the filing date of the instant application was very small (fewer than 10 members). In addition,

as noted above, LHR, TSHR, and FSHR all bind peptide hormones. The total number of peptide hormones that were known as of the filing date of the instant application was also very small, i.e., approximately 50. Thus, it was concluded that LGR7 also binds a hormone; that the ectodomain would be useful as an LGR7 antagonist; and that LGR7 could be used to identify LGR7 agonists and antagonists. In view of the well-known structure of LHR, TSHR, and FSHR, and the overall structural similarity of LGR7 to LHR, TSHR, and FSHR, at least one specific, substantial, and credible utility for the claimed invention would have been readily apparent to one of skill in the art in view of the disclosure, alone or taken with the knowledge of one skilled in the art.

Conclusion as to the rejection under 35 U.S.C.§101

The instant invention as claimed has a well established asserted utility, because at least one specific, substantial, and credible utility for the claimed invention would have been readily apparent to one of skill in the art in view of the disclosure, alone or taken with the knowledge of one skilled in the art. Furthermore, the instant invention as claimed has an asserted utility that is specific, substantial, and credible.

II. WHETHER CLAIMS 1, 2, 4, 7-11, AND 18-20 MEET THE ENABLEMENT REQUIREMENT OF 35 U.S.C. §112, FIRST PARAGRAPH

Claims 1, 2, 4, 7-11, and 18-20 were rejected under 35 U.S.C.§112, first paragraph, as allegedly lacking enablement. In support of this rejection, the Office argued that since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention. The rejection of claims 1, 2, 4, 7-11, and 18-20 as allegedly lacking enablement is in error.

Claims 1, 2, 4, 8-11, and 18-20 were rejected under 35 U.S.C.§112, first paragraph, as allegedly lacking enablement. In support of this rejection, the Office argued that the specification does not teach the functional characteristics of LGR7 or any polynucleotide variants; and that undue experimentation would be required by the skilled artisan to generate the infinite number of LGR7 variants recited in the claims and to

screen the same for activity. The rejection of claims 1, 2, 4, 8-11, and 18-20 as allegedly lacking enablement is in error.

Claims 1, 2, 4, 7-11, and 18-20

The final Office Action stated that "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention." Final Office Action, page 7.

As discussed in ample detail above, the claimed invention complies with the utility requirement of 35 U.S.C.§101. Accordingly, this rejection is rendered moot.

Claims 1, 2, 4, 8-11, and 18-20

The Advisory Action stated that the specification does not teach the functional characteristics of LGR7 or any polynucleotide variants.

The specification teaches LGR7 nucleic acid and polypeptide variants.

The specification discusses various polypeptide fragments of LGR7. Specification, page 9, line 5 to page 11, line 17. Furthermore, the specification provides the nucleotide and amino acid sequences of at least two LGR7 polypeptides. As shown in Figure 5, the polynucleotides identified as SEQ ID NO:05 and SEQ ID NO:07 encode the polypeptides identified as SEQ ID NO:06 and 08, respectively. Both SEQ ID NO:06 and 08 are LGR7 polypeptides. The specification states that the LGR7 polypeptides are encoded by splice variants. Specification, page 25, lines 15-25. As noted above, the specification states that LGR7 binds a hormone.

The specification teaches fragments of LGR7 and discusses the functional characteristics of such fragments.

The specification discusses the extracellular domain of LGR7, and states that this ectodomain is useful, e.g., in the neutralization of the action of endogenous ligands. Specification, page 11, lines 1-4; and

page 21, lines 12-15. The specification discusses the structure of LGR7, and states that LGR7 contains a leucine-rich repeat-containing ectodomain. Specification, page 25, lines 15-19. Figure 6 of the instant application shows an alignment of LGR4, LGR5, LHR, FSHR, and TSHR, and shows the position of the ectodomain. It would require nothing more than the skill of one ordinarily skilled in the art to include LGR7 in the alignment to determine the ectodomain. Indeed, Hsu (2002) did just that, and generated a soluble LGR7 ectodomain. As discussed above, Hsu (2002) demonstrated that a soluble extracellular domain of LGR7 functions as an antagonist to LGR7, neutralizing the action of the ligand relaxin. Thus, those skilled in the art, given the guidance in the specification, would know which fragments of LGR7 would be expected to function as discussed in the specification.

Based on the guidance in the specification, those skilled in the art could make variants of LGR7 and predict their function.

Based on the alignments provided in Figure 6, those skilled in the art could readily determine, without undue experimentation, those amino acids of LGR7 that could be altered without changing the function of LGR7, and those amino acid residues that could be altered to result in a change of LGR7 function. The fact that those skilled in the art could readily identify amino acid residues essential for function is demonstrated in Hsu (2000). Hsu (2000) states that, based on an alignment of the LGR7 amino acid sequence with those of other hormone-binding GPCR, point mutations were made in LGR7 that affected its function as a GPCR. Hsu (2000), page 1261, column 2, second full paragraph, to page 1263, column 2, end of Results section. Thus, given the information provided in the instant specification, those skilled in the art could readily and without undue experimentation identify and mutate amino acid residues important for the function of an LGR7 polypeptide as a GPCR.

The final Office Action cited various references to support the assertion that predicting protein and DNA structure from sequence data is problematic. However, as noted above, Appellants showed that the amino acid sequence of LGR7 could be aligned with the amino acid sequence of other LGR-type GPCR, and amino acids could be successfully identified that altered the function, or that had no effect on the function, of LGR7. Accordingly, those skilled in the art could, without undue experimentation, do exactly as Appellants

did, using nothing more than the information provided in the specification, and identify, make, and use LGR7 variants.

The Advisory Action stated that undue experimentation would be required by the skilled artisan to generate the infinite number of LGR7 variants recited in the claims and to screen the same for activity.

The courts have clearly taught that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. For example, see MPEP §2164.01.[16]

As the court explained[17]:

> "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed."

Practitioners in the chemical molecular biology arts frequently engage in extensive modification of reaction conditions and complex and lengthy experimentation where many factors must be varied to succeed in performing an experiment or in producing a desired result. The Federal Circuit has found that such extensive experimentation is not undue in the molecular biology arts. For example, the court concluded that extensive screening experiments, while being voluminous, were not undue in view of the art which routinely performs such long experiments.[18]

The skill level in the art is high. The relevant ordinarily skilled artisan is generally a skilled laboratory technician with experience in molecular biology and/or a scientist with the equivalent of a doctoral degree, and experience with molecular biology techniques. Furthermore, such artisans are required to keep abreast of the latest technology through continuing education and reading of scientific journal articles. As such, the skill level of those developing and using methods for manipulating DNA, producing a protein encoded by the DNA, and performing functional assays on the encoded protein, was high as of the priority date of the instant application.

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16 See also *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 227 USPQ 428 (Fed. Cir. 1985).
17 *In re Wands* 8 USPQ 2d at 1404

Indeed, as discussed above, the fact that those skilled in the art, given the information in the instant application in combination with the general knowledge in the art, could readily identify amino acid residues essential for function is demonstrated in Hsu (2000). Hsu (2000), carrying out nothing more than routine experimentation, identified amino acid residues essential for function of the LGR7. Thus, given the information provided in the instant specification, combined with the skill and knowledge in the art, those skilled in the art could readily and without undue experimentation identify and mutate amino acid residues important for the function of an LGR7 polypeptide as a GPCR.

Furthermore, Hsu (2002), carrying out nothing more than routine experimentation, generated a soluble LGR7 ectodomain, and demonstrated that a soluble extracellular domain of LGR7 functions as an antagonist to LGR7, neutralizing the action of the ligand relaxin. Thus, those skilled in the art, given the guidance in the specification, would know which fragments of LGR7 would be expected to function as discussed in the specification.

Conclusion as to the enablement rejections under 35 U.S.C.§112, first paragraph

Claims 1, 2, 4, 7-11, and 18-20 are not properly rejected under 35 U.S.C.§112, first paragraph, for lack of enablement, on the basis that they lack utility and therefore those skilled in the art would not know how to make and use the claimed invention. As discussed in ample detail above, the instant invention as claimed meets the utility requirement of 35 U.S.C.§101, and as such the claims are not properly rejected under 35 U.S.C.§112, first paragraph, in connection with a utility rejection.

Claims 1, 2, 4, 8-11, and 18-20 meet the enablement requirements of 35 U.S.C.§112, first paragraph. The instant specification provides ample detail as to how to make and use LGR7 nucleic acids as claimed; LGR7 polypeptides as claimed; and methods of screening for an LGR7 ligand, without the need for undue experimentation. Accordingly, claims 1, 2, 4, 8-11, and 18-20 meet the enablement requirements of 35 U.S.C.§112, first paragraph.

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18 *Hybritech v. Monoclonal Antibodies, Inc.* 231 USPQ 81 (Fed. Cir. 1986)

III. WHETHER CLAIMS 1, 2, 4, 8-11, AND 18-20 MEET THE WRITTEN DESCRIPTION REQUIREMENT OF 35 U.S.C. §112, FIRST PARAGRAPH

The Advisory Action stated that the "description of two LGR7 polynucleotides and polypeptides in the specification is not a representative number of embodiments to support the description of an entire genus of functionally equivalent polynucleotides and polypeptides which incorporate all mutants, derivatives, and fragments having at least 80% identity to the nucleic acid sequence of SEQ ID NO:7 and the amino acid sequence of SEQ ID NO:8." Advisory Action, page 3. The rejection of claims 1, 2, 4, 8-11, and 18-20 as allegedly lacking written description is in error.

The Written Description Guidelines

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. §112, paragraph 1 "Written Description" Requirement (Federal Register 66, No. 4, January 5, 2001; hereinafter the "Written Description Guidelines") provides instructions for examining patent applications for compliance with the written description requirement of 35 U.S.C.§112, first paragraph.

The Written Description Guidelines state:

(1) There is a strong presumption that an adequate written description of the claimed invention is present when the application is filed;

(2) The Examiner has the initial burden of presenting evidence or reasons why a person skilled in the art would not recognize that the written description of the invention provides support for the claims;

(3) Consequently, rejection of an original claim for lack of written description should be rare;

(4) An Examiner should review the entire application to understand how Applicant provides support for the claimed invention; and

(5) Such a review is conducted *from a standpoint of one of skill in the art at the time the application was filed and should include a determination of the field of the invention and the level of skill and knowledge*

in the art (emphasis added).[19]

As stated in the Written Description Guidelines, "In most technologies which are mature, and *wherein the knowledge and level of skill in the art is high*, a written description question **should not be raised** for original claims even if the specification discloses only a method of making the invention and the function of the invention." Written Description Guidelines, page 1106, emphasis added. The Written Description Guidelines are based in part on *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir.1997). It should be remembered that *University of California v. Eli Lilly and Co.*, (Fed. Cir.1997) was based on a patent that was filed in 1977, i.e., over 20 years ago, when the level of skill in the art was not at the level that it was as of the filing date of the instant application.

The Written Description Guidelines state that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species; and that a "representative number of species" means that the species which are adequately described are representative of the entire genus. The Written Description Guidelines state that there may be situations in which one species adequately supports a genus; and that what constitutes a "representative number" is an inverse function of the skill and knowledge in the art.[20]

The Examiner has not reviewed the instant claims for compliance with the written description requirement in a manner consistent with the Written Description Guidelines.

The Examiner has merely stated that the description of two LGR7 polynucleotides and polypeptides in the specification of the instant application is not a representative number of embodiments to support the description of an entire genus of functionally equivalent polynucleotides and polypeptides. The Examiner has not presented evidence or reasons why a person skilled in the art would not recognize that the written description of the invention provides support for the claims.

19 Written Description Guidelines, at page 1105.
20 Written Description Guidelines, page 1106.

The Examiner has not conducted a review of the claims *from a standpoint of one of skill in the art at the time the application was filed and should include a determination of the field of the invention and the level of skill and knowledge in the art.* Had the claims been examined from the standpoint of one of skill in the art as of the March 26, 1998 priority date of the instant application, the claims could not have reasonably been rejected as lacking adequate written description, because those skilled in the art would have concluded that Appellants had possession of the claimed invention.

The Advisory Action stated that the "description of two LGR7 polynucleotides and polypeptides in the specification is not a representative number of embodiments to support the description of an entire genus of functionally equivalent polynucleotides and polypeptides which incorporate all mutants, derivatives, and fragments having at least 80% identity to the nucleic acid sequence of SEQ ID NO:7 and the amino acid sequence of SEQ ID NO:8." Advisory Action, page 3.

However, as stated in the Written Description Guidelines, what constitutes a "representative number" *is an inverse function of the skill and knowledge in the art.*[21] The Examiner has failed to take into account the level of skill of those in the relevant art as of the March 26, 1998 priority date of the instant application. The skill and knowledge in the art relating to protein sequence, structure, and function was so high as of the March 26, 1998 priority date that, given the instant disclosure, those skilled in the art would immediately recognize that Appellants had in their possession the claimed nucleic acids and polypeptides.

The instant specification provides adequate written description for the claimed invention.

The specification provides the nucleotide and amino acid sequences of at least two LGR7 polypeptides. As shown in Figure 5, the polynucleotides identified as SEQ ID NO:05 and SEQ ID NO:07 encode the polypeptides identified as SEQ ID NO:06 and 08, respectively. Both SEQ ID NO:06 and 08 are LGR7 polypeptides. The specification states that the LGR7 polypeptides are encoded by splice variants. Specification, page 25, lines 15-25. Furthermore, as discussed above, the specification provides a description of various fragments of LGR7 polypeptides, e.g., a soluble ectodomain of LGR7, and uses

21 Written Description Guidelines, page 1106.

thereof. Thus, the specification provides adequate written description for the claimed nucleic acids and polypeptides.

Conclusion as to the rejection under 35 U.S.C.§112, first paragraph

The instant specification provides the nucleotide and amino acid sequences of an adequate number of species, such that those skilled in the art would have recognized that Appellants had, as of the priority date, possession of the claimed invention. In view of such, claims 1, 2, 4, 8-11, and 18-20 meet the written description requirement of 35 U.S.C.§112, first paragraph.

SUMMARY

Conclusion as to the rejection under 35 U.S.C.§101

The instant invention as claimed meets the utility requirement of 35 U.S.C.§101. The instant invention as claimed has a well established utility. At least one specific, substantial, and credible utility for the claimed invention would have been readily apparent to one of skill in the art in view of the disclosure, alone or taken with the knowledge of one skilled in the art. Furthermore, the instant invention as claimed has at least one asserted utility that is specific, substantial, and credible.

Conclusion as to the rejections under 35 U.S.C.§112, first paragraph

- Claims 1, 2, 4, 7-11, and 18-20 are not properly rejected under 35 U.S.C.§112, first paragraph, for lack of enablement, on the basis that they lack utility and therefore those skilled in the art would not know how to make and use the claimed invention. As discussed in ample detail above, the instant invention as claimed meets the utility requirement of 35 U.S.C.§101, and as such the claims are not properly rejected under 35 U.S.C.§112, first paragraph, in connection with a rejection under 35 U.S.C.§101.
- Claims 1, 2, 4, 8-11, and 18-20 meet the enablement requirements of 35 U.S.C.§112, first paragraph. The instant specification provides ample detail as to how to make and use LGR7 nucleic acids as claimed; LGR7 polypeptides as claimed; and methods of screening for an

LGR7 ligand, without the need for undue experimentation. Accordingly, claims 1, 2, 4, 8-11, and 18-20 meet the enablement requirements of 35 U.S.C.§112, first paragraph.

- The instant specification provides the nucleotide and amino acid sequences of an adequate number of species, such that those skilled in the art would have recognized that Appellants had, as of the priority date, possession of the claimed invention. In view of such, claims 1, 2, 4, 8-11, and 18-20 meet the written description requirement of 35 U.S.C.§112, first paragraph.

RELIEF REQUESTED

Appellants respectfully request that the rejection of claims 1, 2, 4, 7-11, and 18-20 under 35 U.S.C. §101, and the rejections of claims 1, 2, 4, 7-11, and 18-20, and of claims 1, 3, 4, 8-11, and 18-20, under 35 U.S.C. §112, first paragraph, be reversed, and that the application be remanded to the Examiner with instructions to issue a Notice of Allowance.

Respectfully submitted,
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Date: May 21, 2004

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APPENDIX OF APPEALED CLAIMS

1. An isolated nucleic acid encoding a mammalian leucine-rich repeat-containing G-protein coupled receptor 7 (LGR7) protein, wherein the LGR7 protein comprises an amino acid sequence having at least 80% amino acid sequence identity to the sequence set forth in SEQ ID NO:08.

2. An isolated nucleic acid according to Claim 1, wherein said mammalian protein has the amino acid sequence of SEQ ID NO:08.

4. An isolated nucleic acid according to Claim 1, wherein the nucleotide sequence of said nucleic acid has the sequence set forth in SEQ ID NO:07 or the complementary sequence thereof.

7. An isolated nucleic acid that hybridizes under stringent conditions at 50°C or higher in a solution of 15 mM sodium chloride, 1.5 mM sodium citrate to a nucleic acid having the nucleotide sequence set forth in SEQ ID NO:07 or the complete complementary sequence thereof.

8. An expression cassette comprising a transcriptional initiation region functional in an expression host, a nucleic acid having a sequence of the isolated nucleic acid according to Claim 1 under the transcriptional regulation of said transcriptional initiation region, and a transcriptional termination region functional in said expression host.

9. A cell comprising an expression cassette according to Claim 8 as part of an extrachromosomal element or integrated into the genome of a host cell as a result of introduction of said expression cassette into said host cell, and the cellular progeny of said host cell.

10. A method for producing a mammalian leucine-rich repeat-containing G-protein coupled receptor 7 (LGR7) protein, wherein the LGR7 protein comprises an amino acid sequence having at least 80% amino acid sequence identity to the sequence set forth in SEQ ID NO:08, said method comprising:

growing a cell according to Claim 9, whereby said mammalian protein is expressed; and

isolating said protein substantially free of other proteins.

11. A purified polypeptide composition comprising a mammalian leucine-rich repeat-containing G-protein coupled receptor 7 (LGR7) protein or a fragment thereof, wherein the LGR7 protein is at least about 80% pure, and wherein the LGR7 protein comprises an amino acid sequence having at least 80% amino acid sequence identity to the sequence set forth in SEQ ID NO:08.

18. A method of screening a sample for the presence of a ligand for leucine-rich repeat-containing G-protein coupled receptor 7 (LGR7) receptor, said method comprising:

contacting said sample with an LGR7 receptor, wherein the LGR7 receptor comprises an amino acid sequence having at least 80% amino acid sequence identity to the sequence set forth in SEQ ID NO:08, and

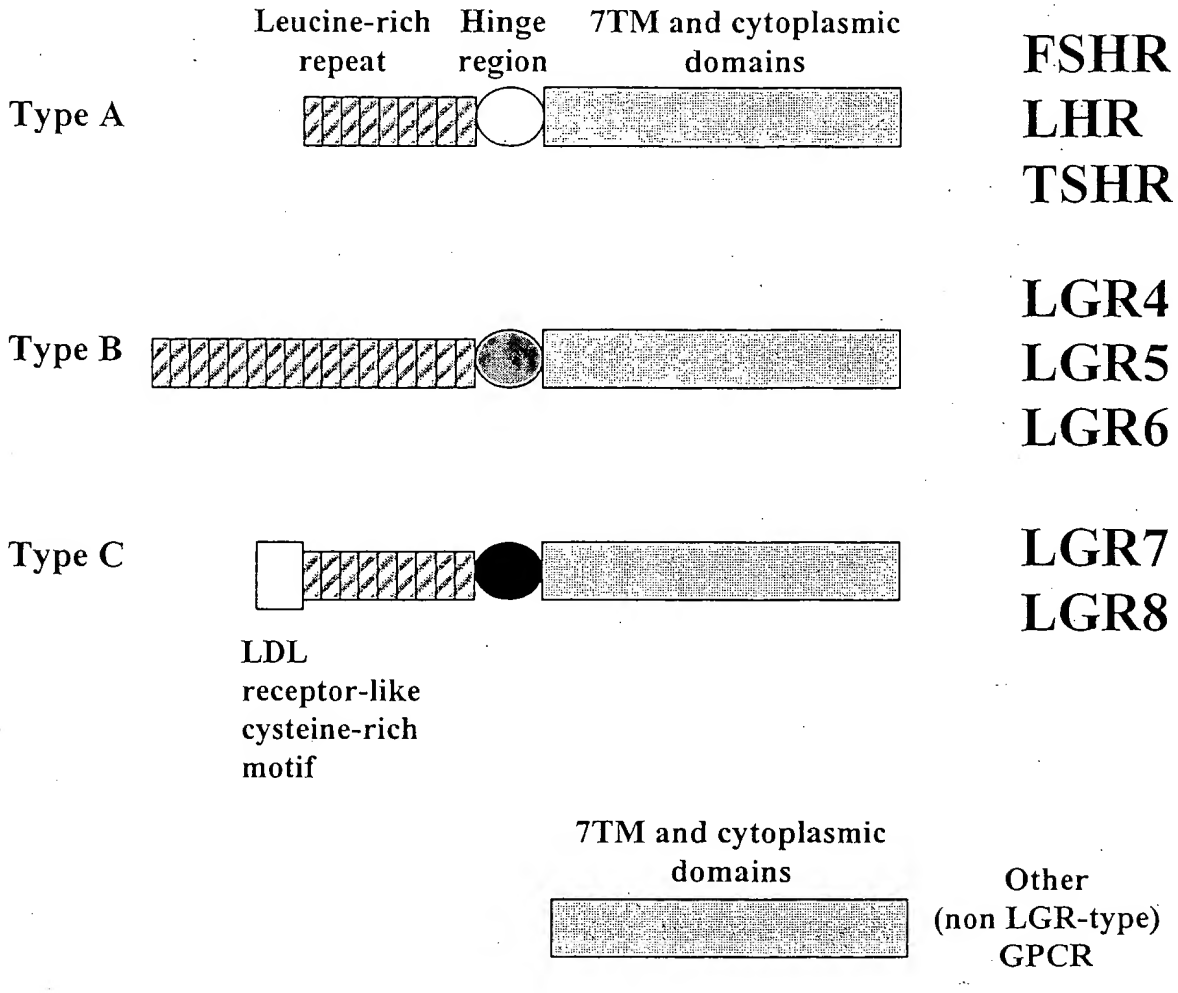
detecting the presence of binding between said receptor and ligand in said sample.

19. The nucleic acid of claim 1, wherein said LGR7 protein comprises an amino acid sequence having at least about 90% amino acid sequence identity to the sequence set forth in SEQ ID NO:08.

20. The nucleic acid of claim 1, wherein said LGR7 protein binds a hormone.

09/647,067
Exhibit 1

Schematic representation of functional domains in LGR family receptors



Alignment of LGR7 with LH receptor
Identities = 148/636 (23%), Positives = 289/636 (45%)

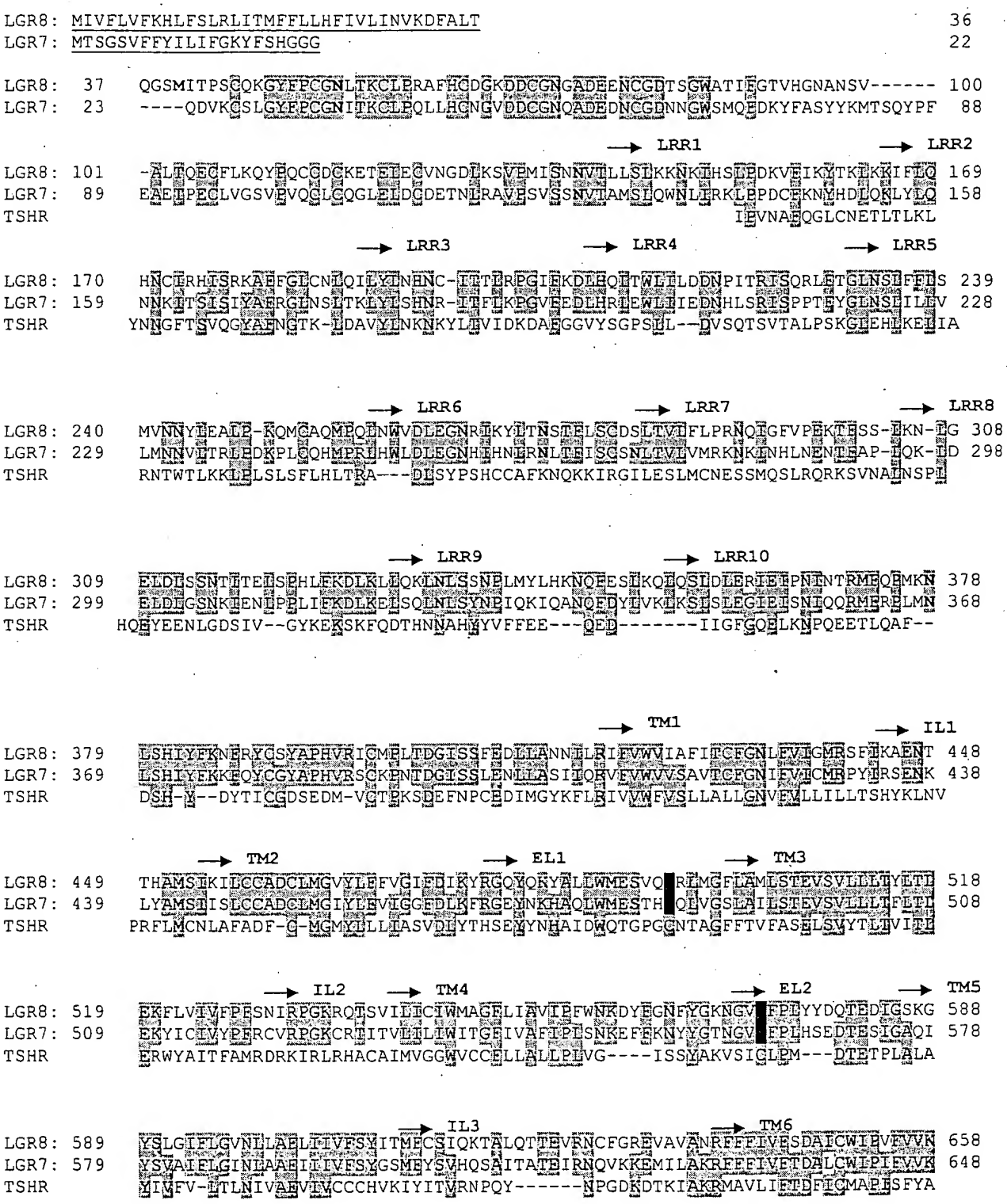
```
LGR7 :  89  EAETPECLVGSVPVQCLCQGLELDCDETNLRAVPSVSSNVTAMSLQWNLIRKLPPDCFKN 148
            EA  PE      P  C+  G  L C        P  ++ +T +SL +  ++ +P   F+
LHR  :  27  EALCPE------PCNCVPDGA-LRC--------PGPTAGLTRLSLAYLPVKVIPSQAFRG  71

LGR7 : 149 YHDLQKLYL-QNNKITSISIYAFRGLNSLTKLYLSHNR-ITFLKPGVFEDLHRLEWLIIE 206
            +++ K+ + Q + +  I   AF  L +L+++ + + + + +++PG F +L  L++L I
LHR  :  72  LNEVIKIEISQIDSLERIEANAFDNLLNLSEILIQNTKNLRYIEPGAFINLPGLKYLSIC 131

LGR7 : 207 DNHLSRISPPT--FYGLNSLILLVLMNNVLTRLPDKPLCQHMPRLHWLDLEGNHIHNLRN 264
           +  + +    T  F   ++ IL +  N  +T +P             L L GN    +++
LHR  : 132 NTGIRKFPDVTKVFSSESNFILEICDNLHITTIPGNAFQGMNNESVTLKLYGNGFEEVQS 191

LGR7 : 265 LTFISCSNLTVLVMRKN-KINHLNENTFAPLQKLDELDLGSNKIENLPPLIFKDLKEL-- 321
             F + + LT L +++N  +  ++   F        LD+ S K++ LP    + ++ L
LHR  : 192 HAF-NGTTLTSLELKENVHLEKMHNGAFRGATGPKTLDISSTKLQALPSYGLESIQRLIA 250

LGR7 : 322 -SQLNLSYNPIQKIQANQFD-------YLVKLKSLSLEGIEISNI--------------- 358
            S  +L   P ++   N  +       +    ++L  +    S+
LHR  : 251 TSSYSLKKLPSRETFVNLLEATLTYPSHCCAFRNLPTKEQNFSHSISENFSKQCESTVRK 310

                                                          ---> TM1
LGR7 : 359 --QQRMFRPLMNLSHIYFKKFQYCGYAPHVRSCKPNTDGISSLENLLASIIQRVFVWVVS 416
             + ++  ++  S +    ++Y    P    C P  D  +  E+++     RV +W+++
LHR  : 311 VSNKTLYSSMLAESELSGWDYEYGFCLPKTPRCAPEPDAFNPCEDIMGYDFLRVLIWLIN 370

LGR7 : 417 AVTCFGNIFVICMRPYIRSENKLYAMSIISLCCADCLMGIYLFVIGGFDLKFRGEYNKHA 476
            +   GN+ V+ +    R +  +    + +L  AD  MG+YL +I   D + +G+Y  HA
LHR  : 371 ILAIMGNMTVLFVLLTSRYKLTVPRFLMCNLSFADFCMGLYLLLIASVDSQTKGQYYNHA 430

LGR7 : 477 QLWMESTHCQLVGSLAILSTEVSVLLLTFLTLEKYICIVYPFRCVRPGKCR-TITVLILI 535
             W   + C   G   + ++E+SV  LT +TLE++  I Y     +  + R  I +++
LHR  : 431 IDWQTGSGCSTAGFFTVFASELSVYTLTVITLERWHTITYAIHLDQKLRLRHAILIMLGG 490

LGR7 : 536 WITGFIVAFIPLSNKEFFKNYYGTNGVCFPLHSEDTESIGAQIYSVAIFLGINLAAFIII 595
           W+   ++A +PL       NY   + +CFP+   D E+  +Q+Y + I + +N+ AF II
LHR  : 491 WLFSSLIAMLPLVG---VSNYMKVS-ICFPM---DVETTLSQVYILTILI-LNVVAFFII 542

LGR7 : 596 VFSYGSMFYSVHQSAITATEIRNQVKKEMILAKRFFFIVFTDALCWIPIFVVKFLSLLQV 655
             Y  ++++V    + AT       K+  +AK+   ++FTD  C  PI      +  +V
LHR  : 543 CACYIKIYFAVRNPELMAT------NKDTKIAKKMAILIFTDFTCMAPISFFAISAAFKV 596

LGR7 : 656 EIPGTITSWVVIFIL--PINSALNPILYTLTTRPFK 689
            +  T+T+  V+ +L  PINS  NP LY + T+ F+
LHR  : 597 PLI-TVTNSKVLLVLFYPINSCANPFLYAIFTKTFQ 631
```

09/647,067
Exhibit 3

Alignment of LGR7 with TSH receptor

```
LGR7 : 106 LPPDCFKNY-HDLQKLDLQNNKITSISIYAFRGLNSLTKLYLSHNR-ITFLKPGVFEDLH 163
           +P + F+  ++     L L NN  TS+  YAF G   L  +YL+ N+ +T +    F  ++
TSHR : 167 IPVNAFQGLCNETLTLKLYNNGFTSVQGYAFNG-TKLDAVYLNKNKYLTVIDKDAFGGVY 225

LGR7 : 164 RLEWLIIEDNHLSRISPPTFYGLNSLILLVLMNN-VLTRLPDKPLCQHMPRLHWLDLE-G 221
               L+  D   + ++     GL  L  L+  N  L +LP      H+ R    DL
TSHR : 226 SGPSLL--DVSQTSVTALPSKGLEHLKELIARNTWTLKKLPLSLSFLHLTRA---DLSYP 280

LGR7 : 222 NHIHNLRN-------LTFISCSNLTVLVMRKNK-INHLNENTFAPLQKLDELDLGSNKIE 273
           +H    +N       L  + C+  ++  +R+ K +N LN    +PL +  E +LG + +
TSHR : 281 SHCCAFKNQKKIRGILESLMCNESSMQSLRQRKSVNALN---SPLHQEYEENLGDSIV- 335

LGR7 : 274 NLPPLIFKDLKELSQLNLSYNPIQKIQANQFDYLVKLKSLSLEGIEISNIQQRMFRPLMN 333
                     KE S+    ++N      A+ + +  + +        EI    Q +  P
TSHR : 336 --------GYKEKSKFQDTHN-----NAHYYVFFEEQED------EIIGFGQELKNPQEE 376

                                                    --> TM1
LGR7 : 334 LSHIYFKKFQY--CGYAPHVRSCKPNTDGISSLENLLASIIQRVFVWVVSAVTCFGNIFV 391
               +   + Y  CG +  +  C P +D  +  E+++     R+ VW VS +    GN+FV
TSHR : 377 TLQAFDSHYDYTICGDSEDM-VCTPKSDEFNPCEDIMGYKFLRIVVWFVSLLALLGNVFV 435

LGR7 : 392 ICMRPYIRSENKLYAMSIISLCCADCLMGIYLFVIGGFDLKFRGEYNKHAQLWMESTHCQ 451
           + +      +  +     + +L  AD  MG+YL +I    DL    EY  HA  W      C
TSHR : 436 LLILLTSHYKLNVPRFLMCNLAFADFCMGMYLLLIASVDLYTHSEYYNHAIDWQTGPGCN 495

LGR7 : 452 LVGSLAILSTEVSVLLLTFLTLEKYICIVYPFRCVRPGKCR-TITVLILIWITGFIVAFI 510
             G    + ++E+SV  LT +TLE++  I  +  R  R  + R    +++  W+  F++A +
TSHR : 496 TAGFFTVFASELSVYTLTVITLERWYAITFAMRLDRKIRLRHACAIMVGGWVCCFLLALL 555

LGR7 : 511 PLSNKEFFKNYYGTNGVCFPLHSEDTESIGAQIYSVAIFLGINLAAFIIIVFSYGSMFYS 570
           PL       + Y    +C P+    DTE+  A  Y V + L +N+ AF+I+    +  ++ +
TSHR : 556 PLVG----ISSYAKVSICLPM---DTETPLALAYIVFV-LTLNIVAFVIVCCCHVKIYIT 607

LGR7 : 571 VHQSAITATEIRNQVKKEMILAKRFFFIVFTDALCWIPIFVVKFLSLLQVEIPGTITSWV 630
           V            N   K+  +AKR   ++FTD +C  PI       ++L   +  T+++
TSHR : 608 VRNPQY------NPGDKDTKIAKRMAVLIFTDFICMAPISFYALSAILNKPLI-TVSNSK 660

LGR7 : 631 VIFIL--PINSALNPILYTLTTRPFKE----MIHRFWYNYRQRKSMDSKGQKTYAHHSSG 684
           ++ +L   P+NS  NP LY + T+ F+      ++ +F     RQ ++   +GQ+    +S+
TSHR : 661 ILLVLFYPLNSCANPFLYAIFTKAFQRDVFILLSKFGICKRQAQAY--RGQRVPPKNSTD 718

LGR7 : 685 VEM 687
           +++
TSHR : 719 IQV 721
```

SEQUENCE ALIGNMENT OF HUMAN LGR7, LGR8, AND TSHR.



```
                          → EL3 → TM7
LGR8: 659   ILSLFRVEIPDTMTSWIVIHFLEVNSALNPILYTLTTNFFKDKLKQLLHKH-QRKSIFKI--KKKSLSTSIV 727
LGR7: 649   FLSLLQVEIEGTITSWVVIFILEINSALNPILYTLITRPFKEMIHRFWYNYRQRKSMDSK--GQKTYAPSFI 718
TSHR      LSATLNKPLITVSNSKILLMLE-YELNSCANEFEYAIFTKAEQRDVFILLSKFGICKRQAQAYRGQRVPPKNST

LGR8: 729   WIEDSSSLKLGVLNKITLGDSIMKPVS*                                          755
LGR7: 719   WVEMWPLQEMPPELMKPDLFTYPCEMSLISQSTRLNSYS*                              757
TSHR        DIQV
```

Signal peptide

```
LGR4   MPGPLGLLCFLALGLLGSAGPSGA  (SEQ ID NO:10)
LGR5   MDTSRLGVLLSLPVLLQLATG  (SEQ ID NO:11)
LHR    MKQRFSALQLLKLLLLLQPPLPRA  (SEQ ID NO:12)
FSHR   MALLLVSLLAFLSLGSG  (SEQ ID NO:13)
TSHR   MRPADLLQLVLLLDLPRDLGG  (SEQ ID NO:14)
```

N-flank cysteine-rich sequence

```
LGR4          APPL AA-P S DGDR----RVD SGKGLTAVPEGLSAFTQA  (SEQ ID NO:15)
LGR5   GSSPRSGVLLRG P-TH H EPDGRMLLRVD SDLGLSELPSNLSVFTSY  (SEQ ID NO:16)
LHR          LREAL P-EP N VPDG--ALR-- PGPTAGLTR  (SEQ ID NO:17)
FSHR               HHRI H SNRVFL----- QESKVTEIPSDLPRNAIE  (SEQ ID NO:18)
TSHR             MG SSPP E HQEED--FRVT KDIQRIPSLPPSTQT  (SEQ ID NO:19)
```

Leucine-rich repeats

```
LGR4   DISMNNITQLPED  KSFPFLEELQLAGN -- SL HPKALSG KE KVLTLQ -- Q
LGR5   DLSMNNISQLLPNPLPSLHFLEELRLAGNA-- TY PKGA TG YS KVLMLQ -- Q
LHR    SLAYLPVKVIPSQ  RGLNEVIKIEISQI S- ER EANA DN LN SEILIQ TK -
FSHR   RFVLTKLRVIQKG  SGFGDLEKIEISQN V- EV EADV SN PK HEIRIEKAN -
TSHR   KLIETHLRTIPSH  SNLPNISRIYVSI- VT QQLESHS YN SKVTHIEIR TR -

LGR4   RTV- SE IHG SA QS RLDA H- TSV EDS--FEGLVQLRH WLD  S-L- EV VR
LGR5   RHV- TE LQN RS QS RLDA H- SYV P-SC-FSGLHSLRH WLD  A-L- E  VQ
LHR    RYIE -G FIN PG KY SIC- TG RKF DVTKVFSSESNFI- EIC  LHI- T  GN
FSHR   LYIN -E FQN PN QY LIS- TG KHL DVHK-IHSLQKVL- DIQ  INIH - ERN
TSHR   TYID -D LKE PL KF GIF- TGLKMF DLTK-VYSTDIFFI EIT  PYM- S  VN

LGR4   PLSN P-TLQA T AL NISSIPDF  T LSS VV H HN K-IKSLSQHC D LDN-LE
LGR5   A RS S-ALQAMT AL KIHHIPDY  G LSSWVV H HN R-IHSLGKKC D LHS-LE
LHR    A QGMNNESVT K YG GFEEVQSH  - GTT TS E KE VHLEKMHNGA R A-TGPK
FSHR   S VG SFESVI W NK GIQEIHNC  - GTQ DE N SD NNLEELPNDV H A-SGPV
TSHR   A QG CNETLT K YN GFTSVQGY  - GTK DAVY NK KYLTVIDKDA G VYSGPS

LGR4   T  LNYNYLDEF Q-AIKA PS KELGFHSNSISVI D-GA GGNPL RTIH - DNPLS
LGR5   T  LNYNNLDEF T-AIRT SN KELGFHSNNIRSI E-KA VGNPS ITIHF- DNPIQ
LHR    T  ISSTKLQAL SYGLESIQR I-ATS-SYSLKKL SRET V-N-- LEAT T -----(SEQ ID NO:22)
FSHR   I  ISRTRIHSL SYGLEN KK R-ARSTYN-LKKL TLEKLVA--- MEAS T -----(SEQ ID NO:23)
TSHR   L  VSQTSVTAL SKGLEH KE I-ARNTWT-LKKL LSLS LH--- TRAD S -----(SEQ ID NO:24)

LGR4   FVGNSAFHNLSDLHCLVIRGASLVQWFPNLTGTVHLESLTLTGTKISSIPDDLCQNQKML
LGR5   FVGRSAFQHLPELRTLTLNGASQITEFPDLTGTANLESLTLTGAQISSLPQTVCNQLPNL
LHR    ------------------------------------------------------------
FSHR   ------------------------------------------------------------
TSHR   ------------------------------------------------------------
```

FIG. 6A

```
LGR4   RTLDLSYNNIRDLPSFNGCRALEEISLQRNQISLIKENTFQGLTSLRILDLSRNLIREIH
LGR5   QVLDLSYNLLEDLPSFSVCQKLQKIDLRHNEIYEIKVDTFQQLLSLRSLNLAWNKIAIIH
LHR    ------------------------------------------------------------
FSHR   ------------------------------------------------------------
TSHR   ------------------------------------------------------------

LGR4   SGAFAKLGTITNLDVSFNELTSFPTEGLNGLNQLK (SEQ ID NO:20)
LGR5   PNAFSTLPSLIKLDLSSNLLSSFPITGLHGLTHLK (SEQ ID NO:21)
LHR    ----------------------------------
FSHR   ----------------------------------
TSHR   ----------------------------------
```

C-flank cysteine-rich sequence

```
LGR4   LVGNFKLKDALAARDFANLRSLSV YAYQ    WGCDSLCKLNTEDNSPQEHSVTKEKGA
LGR5   LTGNHALQSLISSENFPELKVIEM YAYQ    GVCENAYKISNQWNKGDNSSMDDLHKK
LHR    ------------------------ --SH    RNLPTKEQNFSHSISENFSKQCESTVR
FSHR   ------------------------ --SH    ANWRRQISELHPICNKSILRQEVDYMT
TSHR   ------------------------ --SH    KNQKKIRGILESLMCNESSMQSLRQRK

LGR4   TDAANVTSTAENE HS-------------------------------------------
LGR5   DAGMFQAQDERDL DF-------------------------------------------
LHR    KVSNKTLYSSMLA SE-------------------------------------------
FSHR   QTRGQRSSLAEDN SS-------------------------------------------
TSHR   SVNALNSPLHQEY ENLGDSIVGYKEKSKFQDTHNNAHYYVFFEEQEDEIIGFGQELKNP

LGR4   -------------------QIIIH T STGA K   YLLGSWMI (SEQ ID NO:25)
LGR5   ---------LLDFEEDLKALHSVQ S SPGP K   HLLDGWLI (SEQ ID NO:26)
LHR    ------LSGWDYEYGFCLPKTPR- A EPDA N   DIMGYDFL (SEQ ID NO:27)
FSHR   YSRGFDMTYTEFDYDLCNEVVDVT S KPDA N   DIMGYNIL (SEQ ID NO:28)
TSHR   QEETLQAFDSHYDYTICGDSEDMV T KSDE N   DIMGYKFL (SEQ ID NO:29)
```

Transmembrane

```
          TM 1                                  TM 2
LGR4   LTV F FLV LLF LL ILTVFA CSS PASKLFIGLISVSNLLM IYTGILTFL AVSW
LGR5   IGV T AV  LTC AL TSTVFR PLYISPIKL IGVIAAVNMLT VSSAVL G  AF F
LHR    VLI L NI  IMG MT LFVLLT RYK TVPRF MCNLSFADFCM LYLLLI S  SQ K
FSHR   VLI F SI  ITG II LVILTT QYK TVPRF MCNLAFADLCI IYLLLI S  IH K
TSHR   IVV FVSL  LLG VF LLILLT HYK NVPRF MCNLAFADFCM MYLLLI S  LY H

                                TM 3
LGR4   GRFAEFG W E  S  KV  SLA  S  SA FL  LAAV  SVFAKDLMKHGKSSH  QF
LGR5   GSFARHGAW EN V  HVI  LSI     S  FL  LAA   GFSVKYSAKFET APFSSL
LHR    GQYYNHA D Q  S  ST  FT      L  YT  VIT   WHTITYAIHLDQ LR  HA
FSHR   SQYHNYA D Q  A  DA  FT      L  YT  AIT   WHTITHAMQLDC VQ  HA
TSHR   SEYYNHA D Q  P  NT  FT      L  YT  VIT   WYAITFAMRLDR IR  HA
```

FIG. 6B

```
                TM 4                                                    TM 5
LGR4    QVAALLALLGAAVAGCF  FHGGQ SASPL   FPTGETPSLGFTVTLVL  SL  LLMA
LGR5    KVIILLCALLALTM AV  L G K GASPL   LPFGEPSTMG MVALIL  SLC LMMT
LHR     ILIMLGGWLFSSLI ML  V V N MKVSI F MDVETTLSQV ILTILI  VV  FIIC
FSHR    ASVMVMGWIFAFAA LF IF I S MKVSI   MDIDSPLSQL VMSLLV  VL  VVIC
TSHR    CAIMVGGWVCCFLL LL  V I S AKVSI   MDTETPLALA IVFVLT  IV  VIVC

                                                TM 6
LGR4    II T L CNL-EKEDLSENSQSSVI HV W    NCIFFC VA FSFAPLITAIS SPEI
LGR5    IA T L CNL-DKGDLENIW CSMV HI L L  NCILNC VA LSF SLINLTF SPEV
LHR     AC I I FAVRNPELMATNK TKIA KM I    DFTCMA IS FAI AAFKVPL TVTN
FSHR    GC IHI LTVRNPNIVSSSS TRIA RM M    DFLCMA IS FAI ASLKVPL TVSK
TSHR    CCHV I ITVRNPQYNPGDK TKIA RM V    DFICMA IS YAL AILNKPL TVSN

                TM 7
LGR4    M SVTLI F LPA L  V  VF N  (SEQ ID NO:30)
LGR5    I FI LVVV LPA L  L  IL N  (SEQ ID NO:31)
LHR     S VL VL Y INS A  F  AI T  (SEQ ID NO:32)
FSHR    A IL VL H INS A  F  AI T  (SEQ ID NO:33)
TSHR    S IL VL Y LNS A  F  AI T  (SEQ ID NO:34)
```

C-terminal tail

```
LGR4    PK KE WKL KRRVTRKHGSVSVSISSQGGCGEQDFYYDCGMYSHLQGNLTVCDCCESFL
LGR5    PH KE LVS RKQTYVWTRSKHPSLMSINSDDVEKQSCDSTQALVTFTSSSITYDLPPSS
LHR     KT QR FFL LSKFGCCKRRAELYRRKDFSAYTSNCKNGFTGSNKPSQSTLKLSTLHCQG
FSHR    KN RR FFI LSKCGCYEMQAQIYRTETSSTVHNTHPRNGHCSSAPRVTNGSTYILVPLS
TSHR    KA QR VFI LSKFGICKRQAQAYRGQRVPPKNSTDIQVQKVTHDMRQGLHNMEDVYELI

LGR4    LTKPVSCKHLIKSHSCPVLTAASCQRPEAYWSDCGTQSAHSDYADEEDSFVSDSSDQVQA
LGR5    VPSPAYPVTESCHLSSVAFVPCL (SEQ ID NO:36)
LHR     TALLDKTRYTEC (SEQ ID NO:37)
FSHR    HLAQN (SEQ ID NO:38)
TSHR    ENSHLTPKKQGQISEEYMQTVL (SEQ ID NO:39)

LGR4    CGRACFYQSRGFPLVRYAYNLQRVRD (SEQ ID NO:35)
```

FIG. 6C